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EXAMINER	
HA, JULIE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,110	MILLAR, ROBERT PETER	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 12, 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-33,35,37,39-41,43 and 45-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15-26,29-33,35,37,39-41,43 and 45-60* is/are rejected.

7)☒ Claim(s) *13,14,27 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 12, 2008 has been entered. Applicant indicated that amended claims filed on March 12, 2008 be entered and considered for this RCE request. Claims 1-11, 13-33, 35, 37, 39-41, 43, 45-60 are pending in this application and examined on the merits in this office action.

Maintained and Revised Rejections
35 U.S.C. 112, 1st

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-11, 15-26, 29-33, 35, 37, 39-41, 43 and 45-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure

that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of

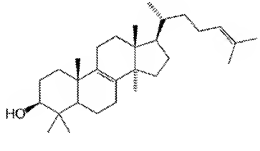
certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a compound comprising a gonadotropin releasing hormone (GnRH) analogue conjugated to a steroid hormone moiety, or a C11, C17, or C21 hydroxy derivative thereof, which is able to bind to a plasma hormone binding protein. The generic statements GnRH conjugated to a steroid hormone moiety, or a C11, C17, or C21 hydroxy derivative thereof do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 1 and 45-46 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of compounds that can form covalent bonds, carbon-carbon bonds, that belong to the same genus of steroid hormone moiety or derivatives thereof. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a steroid hormone molecule that qualify for the functional characteristics claimed as a steroid hormone moiety and derivatives thereof, and other synthetic compounds that can function as a hormone moiety.

The specification is discloses that "derivatives of a hormone moiety include the meaning that the derivatives has been modified from the structure of the hormone moiety found in nature. It may have been modified, for example, to provide a new or

improved site of conjugation to the GnRH analogues, or to improve its stability, or its activity…the derivatives may or may not itself have hormonal activity" (see paragraph [0050] of instant specification US 2006/0247177 A1). The specification discloses that hormone moiety is a steroid hormone moiety…steroid hormone moieties and derivatives thereof are those which possess a suitable atom or functional group for conjugation to a GnRH analogue (see paragraphs [0051]-[0052] of instant specification as described above). The specification further discloses that "preferably, the steroid hormone moiety is estradiol, progesterone, cortisol, corticosterone, estrone, testosterone and dihydroxyestosterone (DHT) (see paragraph [0054] of instant specification as described above). The specification discloses GnRH conjugated to 21-hydroxyprogesterone 21-hemisuccinate and 11-hydroxyprogesteron 11-succinate (see FIG 1A and 1B). The specification does not describe any other steroid hormone moiety or derivatives thereof. According to the dictionary.com, a moiety is defined as an indefinite portion, part or share" (see p. 1 for example of definition of moiety, enclosed). This implies that any portion of a steroid hormone is a moiety of steroid hormone. Thus, for example, the structure  is a moiety of steroid  .

Therefore, there are vast numbers of moieties and derivatives of steroid hormones. Description of estradiol, progesterone, cortisol, corticosterone, estrone, testosterone and dihydroxyestosterone (DHT) is not sufficient to encompass numerous other steroid

hormone moieties and derivatives that belong to the same genus. For example, there are varying lengths, varying compositions, and numerous distinct qualities that make up the genus. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

As broad as the genus hormone is, the genus hormone derivatives is even broader. The specification defines derivative of a hormone as a structure modified from the structure of the hormone found in nature that may or may not retain its hormonal activity but does retain its ability to bind to plasma hormone binding protein. The plasma hormone binding proteins described in the specification are globulins such as eortisol binding globulin, sex hormone binding globulin, progesterone binding globulin and serum albumin. Steroid hormone derivatives that retain their ability to bind to these proteins include those which have been modified by adding a hydroxyl group at position 11, 17 or 21 such as 11- α-hydroxyprogesterones and 21-hydroxyprogesterones. The general relationship between structure and the function of binding to plasma hormone binding protein is described in the specification. For example, the specification states that in order to interact with sex hormone binding globulin, a steroid must contain a 17-β-hydroxyl group and that other features, such as the addition of a hydroxyl or a keto group at C 11 and modification of carbon 2, 6, 9 and 11 in the steroid nucleus have negative effects on binding affinity. In contrast, the specification fails to describe the structure, partial structure or guidance on the structure/function relationship for derivatives of hormones and moieties of steroid hormones.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). With the exception of GNRH conjugated to steroid hormones and their derivatives (preferred embodiment of estradiol, progesterone, cortisol, corticosterone, estrone, testosterone and dihydroxyestosterone (DHT)), the skilled artisan cannot envision the detailed chemical structure of the GNRH conjugates. Therefore, only GNRH analogues conjugated to steroid hormones estradiol, progesterone, cortisol, corticosterone, estrone, testosterone and dihydroxyestosterone (DHT), but not the full breadth of the claims, meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

4. Applicant argues that Applicants have amended claims 1, 45 and 46 by further limiting the claims to recite the subgenus "steroid hormone moiety" and in view of the office action acknowledging that the specification provides descriptive support for using steroid hormones and their derivatives (see pp.4-5), that the rejection should be withdrawn.

5. Applicant's arguments have been fully considered, but have not been found persuasive because as mentioned by the Applicant, "steroid hormone moiety" is a subgenus. There are vast numbers of steroid hormones known in the art. According to previous office action, the Examiner stated that "steroid hormone derivatives that retain their ability to bind to these proteins are well-defined in the specification and include those which have been modified by adding a hydroxyl group at position 11, 17 or 21 such as 11-α-hydroxyprogesterones and 21-hydroxyprogesterones" (see p. 5, 12th paragraph, lines 6-9). Further, the Examiner indicated, "the general relationship between structure and function of binding to plasma hormone binding protein is also provided in the specification. For example, the specification states that in order to interact with sex hormone binding globulin, a steroid must contain 17-β-hydroxyl group and that other features, such as the addition of a hydroxyl or a keto group at C11 and modification of carbon 2, 6, 9 and 11 in the steroid nucleus have negative effects on binding affinity" (see p. 5, 12th paragraph, lines 9-14). The specification discloses

"typically, steroid hormones have either a hydroxyl group or a keto group at the 3 position. Many of the steroid hormones have either a hydroxyl group or a keto group at the 17th position. A number of the steroid hormones have a hydroxyl group at the 11 position. Some of the steroid hormones have a hydroxyl group at the 21 position" (see paragraph [0053]). Specification further discloses that "preferably, the steroid hormone moiety is estradiol, progesterone, cortisol, corticosterone, estrone, testosterone and dihydroxytestosterone (DHT)" (see paragraph [0054]). Further, the specification discloses that "derivatives of steroid hormones which are steroids but which no longer have hormonal activity may be used provided that they bind to a plasma hormone binding protein" (see paragraph [0056]). The specification discloses that "for example, as shown in Example 1, conjugation of a GnRH analogue to the 21 position of 21-hydroxyprogesterone maintains the progesterone activity in the conjugate compound. Conversely, if steroid hormone activity was to be eliminated, the GnRH could be conjugated to the keto group at the 3 position" (see paragraph [0064]). The specification does not describe any other steroid hormones than "estradiol, progesterone, cortisol, corticosterone, estrone, testosterone and DHT". However, the specification does not define a "steroid hormone moiety" or a "steroid hormone derivatives". The specification discloses that "by derivatives of a hormone moiety we include the meaning that the derivative has been modified from the structure of the hormone moiety found in nature..." and "derivatives of steroid hormones are steroids but which no longer have hormonal activity". However, there are vast numbers of steroid hormones and their moieties and derivatives, since different modification steps and different moieties can

form derivatives. Therefore, rejection under 112, 1st paragraph written description is maintained.

New Rejection-35 U.S.C. 112, 1st

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 37 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating breast cancer and use of GnRH conjugate compound as a veterinary contraceptive, does not reasonably provide enablement for prevention of all cancers and infertility and all diseases or disorders that lead to infertility. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are

weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention and (5) The breadth of the claims:

The claims are drawn to a method of combating a hormone-dependent disease or condition and infertility comprising administering a compound comprising a GnRH analogue conjugated to a steroid hormone to an individual in need thereof. The dependent claims are drawn to wherein the hormone-dependent disease or condition is hormone-dependent cancer, benign prostatic hypertrophy, endometriosis, uterine fibroids, premenstrual syndrome, polycystic ovarian syndrome, hirsutism, acne vulgaris, precocious puberty, acute intermittent porphyria, cryptoorchidism and delayed puberty. The instant specification discloses that "by combating a disease or condition we include the meaning of alleviating symptoms of the condition (ie palliative use), or treating the disease or condition, or preventing the disease or condition (ie prophylactic use).

(2) The state of the prior art:

In regards to "preventing a cancers", Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted

in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypercalcemia, hyperuricemia, or obstruction…Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis).

Furthermore, arts indicate the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers. Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants…*In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1st paragraph). Gura T (Science, 1997, 278(5340): 1041-1042, encloses 1-5) indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (see p. 1, 2nd paragraph). Furthermore, Gura T indicates that the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft rumors don't behave like naturally occurring tumors in

humans—they don't spread to other tissues, for example (see p. 2, 4th paragraph). Further, when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body (see p. 3, 7th paragraph). Furthermore, Jain RK (Scientific American, July 1994,58-65) indicates that the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them cancers of the lung, breast, colon, rectum, prostate and brain (see p. 58, left most column, 1st paragraph). Further, Jain RK indicates that to eradicate tumors, the therapeutic agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cells…solid cancers frequently impose formidable barriers to such dispersion (see p. 58, bottom of the left most column continuing onto the top of the middle column). Jain RK indicates that there are 3 critical tasks that drugs must do to attack malignant cells in a tumor: 1) it has to make its way into a microscopic blood vessel lying near malignant cells in the tumor, 2) exit from the vessel into the surrounding matrix, and 3) migrate through the matrix to the cells. Unfortunately, tumors often develop in ways that hinder each of these steps (see p. 58, bottom of right most column). Thus, the art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve.

In regards to preventing such disease as endometriosis, the Merck manual indicates that endometriosis is a noncancerous disorder in which functioning endometrial tissue is implanted outside the uterine cavity (see Merck Manual, p. 1 of

Endometriosis). Pelvic pain, pelvic mass, alteration of menses and infertility are typical symptoms and signs. Some women with extensive endometriosis are asymptomatic; some with minimal disease have incapacitating pain (see Merck Manual, p. 2 of Endometriosis). Diagnosis is suspected based on typical symptoms but must be confirmed by biopsy; Imaging procedures are not specific or adequate for diagnosis. They are done to rule out other disorders, they sometimes show the extent of endometriosis (see Merck Manual, p. 2, Endometriosis, "Diagnosis"). The Merck manual indicates that symptomatic treatment begins with NSAIDs; in most patients, endometriosis recurs after treatment is stopped unless ovarian function is permanently and completely ablated (see Merck Manual, p. 3, Endometriosis, "Treatment").

In regards to preventing infertility, the Merck manual indicates that "infertility is inability of a couple to conceive after 1 year of unprotected intercourse." Infertility can be caused by (1) sperm disorders, (2) decreased ovarian reserve or ovulatory dysfunction, (3) tubal dysfunction and pelvic lesions, (4) abnormal cervical mucus, (5) unidentified factors (see Merck Manual, p. 1, Introduction). The Merck manual indicates that abnormal cervical mucus may (1) remain impenetrable to sperm around the time of ovulation, (2) promote sperm destruction, (3) contain antibodies to sperm (see Merck Manual, p. 1, Abnormal Cervical Mucus). Treatment may include intrauterine insemination or drugs to thin the mucus, but neither treatment has been proved effective. The Merck manual further indicates that assisted reproductive techniques involve manipulation of sperm and ova in vitro with the goal of producing an embryo (see Merck manual, p. 1, Assisted Reproductive Techniques). The Merck manual

indicates that in vitro fertilization (IVF) can be used to treat infertility due to oligospermia, sperm antibodies, tubal dysfunction, or endometriosis as well as unexplained infertility (p.1 of Assisted Reproductive Techniques). Additionally, the Merck manual indicates that decreased ovarian reserve may begin to decrease at age 30 or even earlier and decreases rapidly after age 40. Ovarian lesions also decreases reserve. Testing for decreased ovarian reserve is considered for women who are ≥ 35, who have had ovarian surgery, or who have responded poorly to treatments such as ovarian stimulation with exogenous gonadotropins (see Merck manual, p.1, Decreased Ovarian Reserve). The Merck manual indicates that ovulatory dysfunction is most commonly caused by polycyctic ovary syndrome but has many other causes, including hyperprolactinemia, hypothalamic dysfunction, and other disorders that cause anovulatory amenorrhea. According to the Merck manual, ovulatory dysfunction is suspected if menses are absent, irregular, or not preceded by symptoms, such as breast tenderness, lower abdominal bloating, or moodiness. Measuring morning body temperature daily can help determine whether and when ovulation is occurring; this method is often inaccurate and has an error margin of 2 days, however. According to the Merck manual, ovulation can usually be induced with drugs. Furthermore, the Merck manual indicates that when exogenous gonadotropins are used, approximately 95% of women treated with them ovulate, but the pregnancy rate is only 50 to 75% (see Merck manual, pp. 1-2, Ovulatory Dysfunction). Furthermore, the Merck manual indicates that sperm disorder includes defects in quality or quantity of sperm produced and defects in sperm emission. Spermatogenesis occurs continuously; sperm disorders may result in

an inadequate quantity of sperm-too few (oligospermia) or none (azoospermia)- or defects in sperm quality, such as abnormal motility or structure. Spermatogeneis can be impaired by heat, disorders, drugs or toxins, resulting in an inadequate quantity or defective quality of sperm. Other diseases or disorders may also impair sperm emission, such as diabetes, neurologic dysfunction, retroperitoneal dissection and prostatectomy (see Merck manual, p. 1, Sperm disorders). The Merck manual indicates that clomiphene and assisted reproductive techniques are used to treat sperm disorders if clomiphene is ineffective (see Merck manual, p. 3, Sperm disorder). Tubal dysfunction is fallopian tube obstruction or epithelial dysfunction that impairs zygote motility. The Merck manual indicates that all infertility evaluations include assessment of the fallopian tubes. For treatment, pelvic adhesion can be lysed, or pelvic endometriosis can be fulgurated or ablated by laser. Success rates are low, so assisted reproductive techniques are often necessary (see Merck manual, pp. 1-2, Tubal dysfunction and Pelvic Lesions). The Merck manual further indicates that there are unexplained infertility. The Merck manual indicates that controlled ovarian hyperstimulation (COH) can be used to make pregnancy more likely and to achieve it sooner. The pregnancy rate is the same (about 65%) whether in vitro fertilization is used immediately after unsuccessful treatment with clomiphene plus hCG or whether gonadotropins with intrauterine insemination are used next before trying in vitro fertilization (see Merck manual, p. 1, Unexplained infertility).

The art provide guidance as to how to treat cancers and treat infertility and increase the chance of pregnancy, but do not provide guidance as how to determine

individuals who are susceptible to cancers, and who are susceptible to infertility and other diseases that lead to infertility.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to cancers and infertility and other causes that lead to infertility. Since the activity is based on determining the patient population that is susceptible to cancers and infertility, the predictability in the art is low. This is due to the fact that the art has recognized the difficulty in determining the patient population who are susceptible to cancers and infertility.

The claims do not identify the patient population, therefore, the claims imply that anyone can be protected against cancers and infertility. However, the Applicant has not shown who will be susceptible cancers and infertility. There are too many variables between the experimentation, thus, it clearly shows the unpredictability of the art.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The claims recite "a method of combating a hormone-dependent disease or condition". The instant specification discloses that "by combating a disease or condition we include the meaning of alleviating symptoms of the condition (ie palliative use), or treating the disease or condition, or preventing the disease or condition (ie prophylactic use) (see paragraph [0124]). Accordingly, combating implies preventing the disease or condition. The specification discloses plasma protein binding by the competitive binding of steroid conjugates, in the presence of [1,2,6,7-^{3}H]progesterone or [^{3}H]cortisol, to pregnant guinea pig plasma or human pregnant serum (see paragraph [0166] of instant specification US 2006/0247177 A1). Working Example 1 describes synthesis of GnRH-hormone conjugates. Working example 1 discloses 11 α-hydroxyprogesterone or 21-hydroxyprogesterone (see Example 1). Example 2 discloses treatment of breast cancer with GnRH conjugated to 21-hydroxyprogesterone via a succinate linking group at a dosing quantity and frequency. Example 3 discloses the use of GnRH conjugate compound as a veterinary contraceptive. The specification does not disclose how to prevent cancers and infertility. The specification discloses the treatment of breast cancer and the use of GnRH conjugated compound as a contraceptive. Additionally, it is unclear as to when the compound is to be administered and the patient population to prevent cancers and infertility. As stated above, the specification does not disclose how to prevent cancers and infertility and other disease or disorders that lead to infertility. The working examples are limited to breast cancer and infertility already diagnosed.

As described supra, the Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypocalcaemia, hyperuricemia, or obstruction…Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis).

Furthermore, arts indicate the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers. Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants…*In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test

sites are not typical of the *in vivo* reality (see p. 167, left column, 1st paragraph). Gura T (Science, 1997, 278(5340): 1041-1042, encloses 1-5) indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (see p. 1, 2nd paragraph). Furthermore, Gura T indicates that the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft rumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues, for example (see p. 2, 4th paragraph). Further, when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body (see p. 3, 7th paragraph). Furthermore, Jain RK (Scientific American, July 1994,58-65) indicates that the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them cancers of the lung, breast, colon, rectum, prostate and brain (see p. 58, left most column, 1st paragraph). Further, Jain RK indicates that to eradicate tumors, the therapeutic agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cells…solid cancers frequently impose formidable barriers to such dispersion (see p. 58, bottom of the left most column continuing onto the top of the middle column). Jain RK indicates that there are 3 critical tasks that drugs must do to attack malignant cells in a tumor: 1) it has to make its way into a microscopic blood vessel lying near malignant cells in the tumor, 2) exit from the vessel into the surrounding matrix, and 3) migrate through the matrix to the cells. Unfortunately, tumors

often develop in ways that hinder each of these steps (see p. 58, bottom of right most column). Thus, the art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve.

In regards to preventing such disease as endometriosis, the Merck manual indicates that endometriosis is a noncancerous disorder in which functioning endometrial tissue is implanted outside the uterine cavity (see Merck Manual, p. 1 of Endometriosis). Pelvic pain, pelvic mass, alteration of menses and infertility are typical symptoms and signs. Some women with extensive endometriosis are asymptomatic; some with minimal disease have incapacitating pain (see Merck Manual, p. 2 of Endometriosis). Diagnosis is suspected based on typical symptoms but must be confirmed by biopsy; Imaging procedures are not specific or adequate for diagnosis. They are done to rule out other disorders, they sometimes show the extent of endometriosis (see Merck Manual, p. 2, Endometriosis, "Diagnosis"). The Merck manual indicates that symptomatic treatment begins with NSAIDs; in most patients, endometriosis recurs after treatment is stopped unless ovarian function is permanently and completely ablated (see Merck Manual, p. 3, Endometriosis, "Treatment").

In regards to preventing infertility, the Merck manual indicates that "infertility is inability of a couple to conceive after 1 year of unprotected intercourse." Infertility can be caused by (1) sperm disorders, (2) decreased ovarian reserve or ovulatory dysfunction, (3) tubal dysfunction and pelvic lesions, (4) abnormal cervical mucus, (5) unidentified factors (see Merck Manual, p. 1, Introduction). The Merck manual indicates that abnormal cervical mucus may (1) remain impenetrable to sperm around the time of

ovulation, (2) promote sperm destruction, (3) contain antibodies to sperm (see Merck Manual, p. 1, Abnormal Cervical Mucus). Treatment may include intrauterine insemination or drugs to thin the mucus, but neither treatment has been proved effective. The Merck manual further indicates that assisted reproductive techniques involve manipulation of sperm and ova in vitro with the goal of producing an embryo (see Merck manual, p. 1, Assisted Reproductive Techniques). The Merck manual indicates that in vitro fertilization (IVF) can be used to treat infertility due to oligospermia, sperm antibodies, tubal dysfunction, or endometriosis as well as unexplained infertility (p.1 of Assisted Reproductive Techniques). Additionally, the Merck manual indicates that decreased ovarian reserve may begin to decrease at age 30 or even earlier and decreases rapidly after age 40. Ovarian lesions also decreases reserve. Testing for decreased ovarian reserve is considered for women who are ≥ 35, who have had ovarian surgery, or who have responded poorly to treatments such as ovarian stimulation with exogenous gonadotropins (see Merck manual, p.1, Decreased Ovarian Reserve). The Merck manual indicates that ovulatory dysfunction is most commonly caused by polycyctic ovary syndrome but has many other causes, including hyperprolactinemia, hypothalamic dysfunction, and other disorders that cause anovulatory amenorrhea. According to the Merck manual, ovulatory dysfunction is suspected if menses are absent, irregular, or not preceded by symptoms, such as breast tenderness, lower abdominal bloating, or moodiness. Measuring morning body temperature daily can help determine whether and when ovulation is occurring; this method is often inaccurate and has an error margin of 2 days, however. According to

the Merck manual, ovulation can usually be induced with drugs. Furthermore, the Merck manual indicates that when exogenous gonadotropins are used, approximately 95% of women treated with them ovulate, but the pregnancy rate is only 50 to 75% (see Merck manual, pp. 1-2, Ovulatory Dysfunction). Furthermore, the Merck manual indicates that sperm disorder includes defects in quality or quantity of sperm produced and defects in sperm emission. Spermatogenesis occurs continuously; sperm disorders may result in an inadequate quantity of sperm-too few (oligospermia) or none (azoospermia)- or defects in sperm quality, such as abnormal motility or structure. Spermatogeneis can be impaired by heat, disorders, drugs or toxins, resulting in an inadequate quantity or defective quality of sperm. Other diseases or disorders may also impair sperm emission, such as diabetes, neurologic dysfunction, retroperitoneal dissection and prostatectomy (see Merck manual, p. 1, Sperm disorders). The Merck manual indicates that clomiphene and assisted reproductive techniques are used to treat sperm disorders if clomiphene is ineffective (see Merck manual, p. 3, Sperm disorder). Tubal dysfunction is fallopian tube obstruction or epithelial dysfunction that impairs zygote motility. The Merck manual indicates that all infertility evaluations include assessment of the fallopian tubes. For treatment, pelvic adhesion can be lysed, or pelvic endometriosis can be fulgurated or ablated by laser. Success rates are low, so assisted reproductive techniques are often necessary (see Merck manual, pp. 1-2, Tubal dysfunction and Pelvic Lesions). The Merck manual further indicates that there are unexplained infertility. The Merck manual indicates that controlled ovarian hyperstimulation (COH) can be used to make pregnancy more likely and to achieve it sooner. The pregnancy

rate is the same (about 65%) whether in vitro fertilization is used immediately after unsuccessful treatment with clomiphene plus hCG or whether gonadotropins with intrauterine insemination are used next before trying in vitro fertilization (see Merck manual, p. 1, Unexplained infertility).

The specification has not provided guidance in the way of a disclosure as how to determine individuals that need protection against cancers and infertility. There is no clear guidance as to how to determine the patient population, since cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age, and it is unclear who would develop cancers and infertility, more guidance is necessary. There are other diseases that can lead to such disorder as sperm disorders (diabetes for example) which also leads to infertility. The specification has not provided guidance in the way of a disclosure as how to determine individuals that need protection against sperm disorder (for example, due to diabetes), there is no clear guidance as how to prevent infertility. Since the prior art is still unclear as to who are susceptible to cancers and infertility, more guidance is necessary.

(8) The quantity of experimentation necessary:

Since it is uncertain to predict the patient population who are susceptible for cancers and infertility and other diseases or disorders that lead to infertility, and the Applicant have not provided the appropriate time frame at which the compound should

be administered, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the CXCR4 antagonist peptides would be effective in preventing cancers and rheumatoid arthritis.

Please note that the term "prevent" in an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat" or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes)-including preventing such disorders as cancers and infertility, which is clearly not recognized in the medical art as being totally preventable condition.

35 U.S.C. 112, 2nd

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-11, 15-26, 29-33, 35, 37, 39-41, 43 and 45-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Claims 1, 45 and 46 recite, "steroid hormone moiety, or a C11, C17 or C21 hydroxy derivative thereof". It is unclear what is encompassed by steroid hormone moiety. According to the dicitionary.com, a moiety is defined as "an indefinite portion, part or share" (see p. 1 for example of definition of moiety, enclosed). The specification does not fully define what is meant by a steroid hormone moiety. Therefore, it is unclear what

is encompassed within steroid hormone moiety. Additionally, it is unclear what is meant by C11, C17 or C21 hydroxy derivative, because for example, progesterone does not have a hydroxyl at C11, C17 or C21. Further, claims 1 and 45-46 indicate that C11, C17 or C21 already has a hydroxyl groups, and these groups are modified with the GnRH analogs. Therefore, the claims are indefinite. Because claims 2-11, 15-26, 29-33, 35, 39-42, 43 and 47-60 depend from indefinite claims 1 and 45-46 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Conclusion

10. Claims 13-14 and 27-28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. H./
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654